Argonne National Laboratory
Mathematics and Computer Science Division

Pattern Formation, Self-Organization, and Self-Assembly of Microtubules

February 2005

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Project Summary

How do seemingly random mixtures of molecular components organize themselves into large-scale cellular structures? Can we model this process mathematically, can we simulate it computationally, and what can we learn about the process of self-assembly? We propose to address these questions by studying the mechanism of self-assembly in a system of microtubules and molecular motors.

Recent *in vitro* experiments have shown that a system of microtubules and molecular motors is capable of sustaining a surprising variety of large-scale two-dimensional structures (asters, vortices, and other defects). We claim that the phenomenon of self-organization is evidence of an underlying multiscale process, where nonlinear interactions on a microscopic scale result in the emergence of coherent structures on the macroscopic scale. We propose to study this phenomenon as a problem on three scales. The focus is on the mesoscopic scale, where a master equation describes the evolution of the density of microtubules as a function of position and angular orientation. At this level, the molecular motors enter implicitly through the pairwise interaction of the microtubules. The actual form of the interaction kernel is determined from first principles and validated by molecular dynamics simulations on the microscopic scale. Large-scale structures are studied on the macroscopic scale through a reduced set of equations derived from the master equation. A simple model based on this multiscale approach exhibits an orientational instability at sufficiently large mean densities of the molecular motors. Moreover, the orientational instability leads to the formation of vortices and asters, in agreement with the experiments. We propose various generalizations to bring this simple model closer to a real system of motors and microtubules, and we intend to perform extensive numerical simulations.

Applications. The potential impact of the proposed project extends over various disciplines. The project is motivated by a central problem of biology, namely, the emergence of large-scale coherent structures. The medium we have chosen to study this problem (microtubules and molecular motors) is biologically significant. The results of the proposed study will enhance our understanding of experimental results and will stimulate further research in meaningful and interesting directions. The proposed project will benefit the new discipline of computational science. The proposed problem is a fascinating multiscale problem, with significant computational complexity at several levels. The integration of numerical simulations at the different levels will be a major challenge, and lessons learned here will be applicable to other problems of computational science. A close interaction with the developers of important software packages, such as PETSc, will provide feedback that will benefit their future development. Impact on physics can be expected because molecular dynamics simulations are an integral part of the project. Lessons learned in the project will advance the case for integration of molecular dynamics simulation codes in future multiscale environments. The project will have educational benefits as well because it involves graduate students and a junior researcher.

Pattern Formation, Self-Organization, and Self-Assembly of Microtubules

Project Description

How do seemingly random mixtures of molecular components organize themselves into large-scale cellular structures? Can we model this process mathematically, can we simulate it computationally, and what can we learn about the process of self-assembly? We propose to address these questions by studying the mechanism of self-assembly in a hierarchical biological system composed of microtubules and molecular motors.

Microtubules are hollow polar filaments that are self-assembled from tubulin dimers (a globular protein). Figure 1 shows a three-dimensional view; the tubulin dimers are the beadlike structures. Microtubules act like conveyer belts inside cells. They move vesicles, granules, organelles such as mitochondria, and chromosomes via special attachment proteins. They may work alone or join with other proteins to form more complex structures such as cilia, flagellae, or spindles.

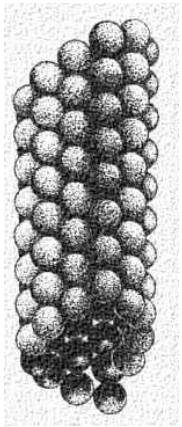

Figure 1: Three-dimensional view of a microtubule.

Molecular motors are proteins that do mechanical work through the hydrolization of adenosine triphosphate (ATP, the energy source of the living cell). This mechanical work is used to move the molecular motor along a microtubule in a direction determined by the polarity of the filament. (For example, kinesin motors move toward microtubule "plus" ends, dynein motors toward "minus" ends.) The motion may have a transport function, or it may apply a force to the microtubule for cell motility and cell division, as in mitosis.

Recent *in vitro* experiments with purified motors and microtubules in thin microchambers [1, 2] have shown a surprising variety of large-scale two-dimensional structures, including *asters*, patterns where all filaments are oriented radially, and *vortices*, patterns where all filaments are oriented at some angle with respect to the radial direction; see Fig. 2. The final structure depends on the relative concentrations of the molecular components. The experiments also indicated that the final structure can be reached through different assembly "pathways" and that dynamic transitions from one state to another can be induced by varying the kinetic parameters.

Large-scale structures such as those observed in the experiments arise through a process of *self-organization*, where the interaction of nonlinear processes on the microscopic scale induce emergent coherent behavior on the macroscopic scale. Under the appropriate circumstances, this coherent behavior manifests itself in observable static or dynamic patterns. Thus, microtubules and molecular motors constitute an interesting and accessible medium to study a central problem in biology, namely, the origin of complex macroscopic structures.

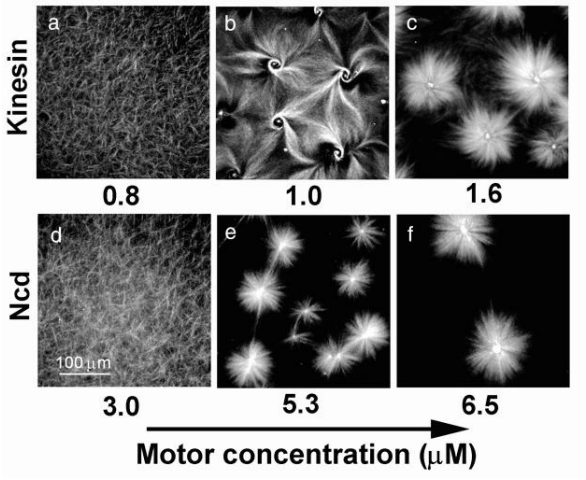

Figure 2: Self-assembled patterns observed in kinesin (top) and Ncd (bottom) for different concentrations of molecular motors [2].

1 Self-Organization

The self-assembly of microtubules into macroscopic structures is an example of *self-organization in energy-dissipating systems*. The system does not evolve toward thermodynamic equilibrium; however, it can produce stable steady and dynamic states. The eventual structure is determined by a variety of parameters, including the concentration of the microtubules, the concentrations of the various types of molecular motors, their processivity, and the time they spend bound at the microtubule ends.

1.1 Mathematical Models

The experimental observation of self-assembly in highly simplified biological systems [1, 2] provided a strong stimulus for theoreticians to devise mathematical models and support the experimental findings with theoretical arguments.

The first computational results on the self-assembly of microtubules were reported in the late 1990s by Leibler and collaborators at Princeton [1, 2], who used a simplified molecular dynamics model.

Lee and Kardar [3] proposed a phenomenological model, which included the transport of molecular motors along microtubules and alignment of microtubules mediated by the molecular motors. Numerical simulations showed patterns including vortices and asters; however, at sufficiently high densities of the molecular motors, the model generated vortex configurations consisting of only a single large vortex.

Kim et al. [4] generalized the phenomenological model of Ref. [3] by including separate densities

of free and bound molecular motors, as well as the density of microtubules. They found a mixed pattern of asters and vortices at low motor densities, which gave way to one of vortices alone as the motor density was increased. This finding was in direct contradiction with experimental evidence [5], which indicated that asters give way to vortices as the motor density is decreased. The model of Ref. [4] was revisited recently by Sankararaman et al. [6], who confirmed the conclusions of Ref. [4].

A different approach was proposed by Kruse et al. [7]. These authors postulated that a mixture of microtubules and molecular motors can be considered as an active viscoelastic material obeying a generalized flux–force relation. While the authors obtained vortex and aster solutions, their model has a large number of unknown parameters and is difficult to analyze.

Liverpool and Marchetti [8] derived a set of equations for the density and orientation of microtubules by averaging the conservation law for their probability distribution function. In the case of homogeneous microtubule distributions, however, their model does not exhibit any orientation transition. Moreover, the model does not adequately describe the density instability, as was pointed out recently by Ziebert and Zimmermann [9].

Recently, we pioneered a different approach [12], one that views the phenomenon of self-assembly in a mixture of microtubules and molecular motors as the manifestation of a *multiscale process*. The approach is anchored at the mesoscopic scale, between the microscopic and macroscopic scales; see Fig. 3. On the mesoscopic scale, the microtubules are modeled as polar filaments,

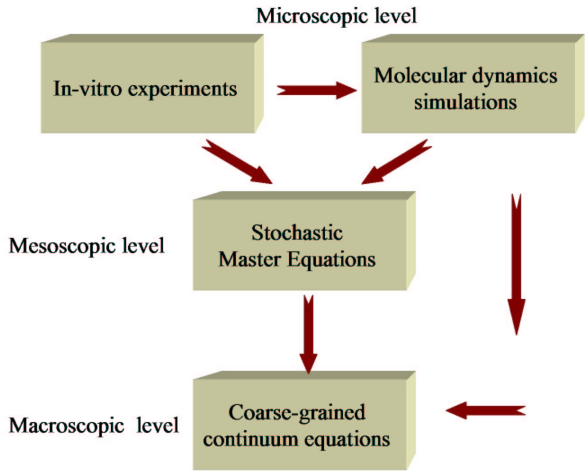

Figure 3: Block diagram illustrating the multiscale concept. The arrows on the right represent the equation-free approach mentioned in Section 2.2.

while the molecular motors enter implicitly through the pairwise interaction of the filaments. In the absence of molecular motors, the microtubules do not interact. In addition, the microtubules may diffuse, and they can be subject to external forces. The fundamental equation is a *master equation* for the evolution of the spatial and orientational distribution of the polar filaments. The kernel describing the pairwise interaction of microtubules is assumed to be known; its precise form is determined from first principles and validated by molecular dynamics simulations on the micro-

scopic scale, where both microtubules and molecular motors are accounted for. The approach is thus reminiscent of the approach taken in the kinetic theory of gases [10, 11], where one studies a distribution function in phase space, whose moments with respect to the velocity correspond to macroscopic observables, such as the density, hydrodynamic velocity, and temperature of the gas. The master equation is, in fact, the link between the microscopic scale, where the details of the interactions between microtubules and molecular motors are worked out, and the macroscopic scale, where the large-scale structures and the dynamics of the orientational moments of the distribution function are observed.

Preliminary investigations [12] have shown that a mathematical model based on this multiscale approach to self-organization exhibits an orientational instability at sufficiently large mean densities, which was missing in the model of Ref. [8]. Moreover, the orientational instability leads to the formation of vortices and asters, in agreement with the experiments.

1.1.1 Prototype Model

We demonstrate the principle of self-organization of microtubules on a prototype model. The model is sufficiently simple to explain the salient phenomena and, at the same time, typical of the more complex phenomena that we propose to study. In this model, the microtubules are represented by thin stiff rods. The rods interact pairwise, and the molecular motors enter the model implicitly through the details of the interaction mechanism.

Assume that the rods lie in a plane. They have the same length l and diameter $d \ll l$, so each rod is fully characterized by the position of its center of mass and its in-plane orientation with respect to a fixed direction. The spatial density of the rods is uniform, but their angular distribution changes with time, because of rotational diffusion and pairwise interactions among the rods. The rules governing the interaction of two rods are the same everywhere: interactions are instantaneous and totally inelastic. Because of the interaction with the molecular motors, the orientation of each of the two rods changes instantaneously to the average of their initial orientations; see Fig. 4. The more general case of inelastic but not totally inelastic interactions can be handled similarly.

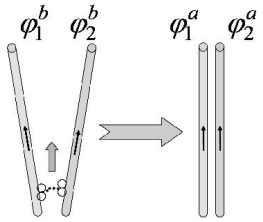

Figure 4: Schematic of the inelastic interaction of two rods.

The present model is similar to the Maxwell model of binary inelastic collisions in the kinetic theory of gases [10, 11], with one important difference. While the Maxwell model concerns a distribution of particle velocities, which can range over the entire space, the present model concerns the distribution of orientation angles, which range over the compact interval $[-\pi, \pi]$. This property allows us to apply the techniques of Fourier analysis.

Let $f(t, \varphi)$ denote the density of rods that are oriented at an angle φ ($-\pi < \varphi < \pi$) at time t ($t > 0$). A straightforward argument leads to the following master equation for the rate of change

of f:

$$\partial_t f = \partial_\varphi^2 f + \int_{-\pi}^{\pi} [f(\varphi + \tfrac{1}{2}\omega) f(\varphi - \tfrac{1}{2}\omega) - f(\varphi + \omega) f(\varphi)]\, d\omega. \tag{1}$$

The first term on the right-hand side represents the effect of rotational diffusion. The integral represents the effect of interactions among the rods, the first term being the gain due to an interaction between two rods with initial orientations $\varphi + \frac{1}{2}\omega$ and $\varphi - \frac{1}{2}\omega$ (resulting in the final orientations φ) and the second term being the loss due to an interaction between two rods, one of which has the initial orientation φ (resulting in orientations other than φ); the integration extends over all possible angles ω. The variables have been made dimensionless by appropriate scalings.

Since f is 2π-periodic in φ, we can decompose f into its Fourier harmonics,

$$f(t, \varphi) = \sum_{k=-\infty}^{\infty} f_k(t) e^{ik\varphi}, \quad f_k(t) = \frac{1}{2\pi} \int_{-\pi}^{\pi} f(t, \varphi) e^{-ik\varphi}\, d\varphi. \tag{2}$$

While f is a microscopic variable, its Fourier coefficients are macroscopic variables, which can be measured. In fact, f_0 is related to the *macroscopic density* ρ, which is defined by the integral

$$\rho(t) = \int_{-\pi}^{\pi} f(t, \varphi)\, d\varphi. \tag{3}$$

Integration of Eq. (1) shows that the master equation preserves the macroscopic density, so ρ and, therefore, f_0 are constant in time. The real and imaginary parts of f_1 represent the *average orientation* of the rods (up to a constant factor ρ),

$$\tau(t) = \frac{1}{2\pi} \int_{-\pi}^{\pi} e^{-i\varphi} f(t, \varphi)\, d\varphi. \tag{4}$$

A straightforward computation yields the following system of equations for the Fourier coefficients:

$$f_k' + (k^2 + \rho) f_k = 2\pi \sum_{m=-\infty}^{\infty} f_m f_{k-m} S((m - \tfrac{1}{2}k)\pi), \quad k = \pm 1, \pm 2, \ldots, \tag{5}$$

where $S(x) = x^{-1} \sin x$. (A prime $'$ denotes differentiation with respect to t.) We reduce this infinite system to a finite system by considering smooth distributions whose Fourier modes with $|k| > 2$ can be ignored:

$$f_1' + \left(1 - 4\pi^{-1} + \rho\right) f_1 = -\tfrac{8}{3} f_1^* f_2, \tag{6}$$

$$f_2' + (4 + \rho) f_2 = 2\pi f_1^2. \tag{7}$$

(A star * denotes complex conjugation.)

Now, suppose that we are interested in the long-time behavior of f and that, on the time scale of interest, the higher harmonic f_2 is essentially in equilibrium. Then Eq. (7) reduces to the algebraic equation $(4 + \rho) f_2 = 2\pi f_1^2$, which can be solved for f_2. If we substitute the result in Eq. (6), we obtain a single equation for f_1,

$$f_1' + \left(1 - 4\pi^{-1} + \rho\right) f_1 = -\tfrac{16}{3} \pi (4 + \rho)^{-1} |f_1|^2 f_1. \tag{8}$$

Notice that the coefficient of f_1 changes sign at a critical value $\rho = \rho_c = 4\pi^{-1} - 1 \approx 3.662$. The trivial solution ($f_1 = 0$) is therefore linearly stable for $\rho < \rho_c$, but as ρ increases, an instability will arise. Near the threshold, the nonlinear term becomes significant, and it will eventually saturate the instability. A good approximation for the coefficient of the nonlinear term near the threshold of instability is $\frac{16}{3}\pi(4+\rho_c)^{-1} \approx 2.18$.

Equation (8) can be rewritten as a Landau equation for the average orientation τ,

$$\tau' = \varepsilon\tau - \alpha|\tau|^2\tau, \tag{9}$$

where $\varepsilon = (4\pi^{-1} - 1)\rho - 1$ and $\alpha = \frac{16}{3}\pi(4+\rho)^{-1}$. Near the threshold of instability, good approximations for the coefficients are $\varepsilon \approx 0.273\rho - 1$ and $\alpha \approx 2.18$, and the evolution of the average orientation is well described by the equation

$$\tau' \quad = \quad (0.273\rho - 1)\tau - 2.18|\tau|^2\tau. \tag{10}$$

This equation, together with the conservation equation $\rho' = 0$, provides a reduced model for the system under consideration, valid near the threshold of instability for the orientation of the rods.

Figure 5 gives the results of some numerical computations. It shows the stationary solution of the master equation (1) for various values of ρ and, in the inset, the corresponding values of $|\tau|^2$ (solid curve). Notice that the rods tend to align as the density increases. For comparison, we also

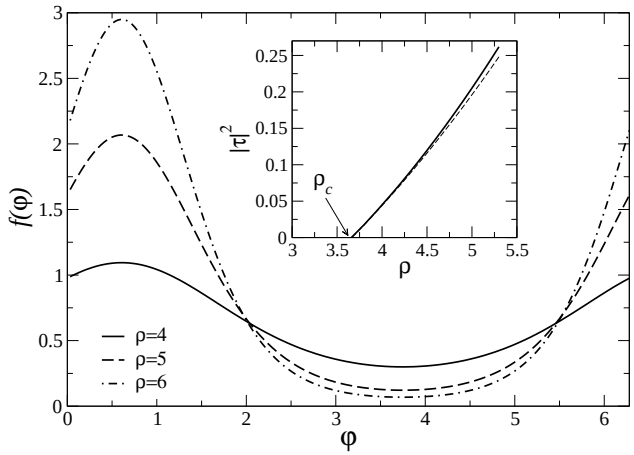

Figure 5: Stationary solutions of Eq. (1) for different values of ρ. Inset: $|\tau|^2$ vs. ρ from Eq. (1) (solid curve) and Eq. (9) (dashed curve).

give the values of $|\tau|^2$ computed from Eq. (9) (dashed curve). The value is exact at the threshold value ρ_c and in close agreement with the true value in a neighborhood of ρ_c.

1.1.2 Realistic Models

The prototype model discussed in the previous section, although far from realistic, already shows two significant characteristics: (i) self-organization through pattern formation—the orientation of the rods shows spontaneous alignment as the density increases, and (ii) modeling at more than one scale—a master equation for the density of the rods at the microscopic level and a reduced equation for their average orientation at the macroscopic level near the threshold of instability. More realistic models will be required to get better insight into the phenomena of pattern formation, self-organization, and self-assembly observed in the experiments. The generalizations must address, among others, the specifics of the interaction of microtubules and molecular motors, as well as the effects of spatial inhomogeneities, the mechanical properties of microtubules, flow effects, and the effects of randomness. We claim that these generalizations exhibit the same or similar instabilities and that these instabilities are critical for the formation of large-scale structures such as the vortices and asters observed in the experiments. Clearly, the demands on the algorithms that we propose for the numerical simulations will increase with the complexity of the models, as will the computational challenges. We address these points in more detail below in Section 2. Here, we discuss various generalizations of the prototype model that we expect to address in the timeframe of the present project.

Localization of Interactions The prototype model does not account for the fact that the outcome of a motor-induced interaction of two microtubules may depend on their mutual distance and orientation prior to the interaction. Realistically, we expect that both factors play a role in the overall behavior of the system.

Assuming that the microtubules are again represented by stiff rods with the same length l and thickness d, we introduce a new independent variable, $x = (x_1, x_2)$, to represent the coordinates of the center of mass of a rod in the plane. The distribution function generalizes to $f(t, x, \varphi)$, and the master equation becomes

$$\begin{aligned} \partial_t f &= \partial_\varphi^2 f + \mathrm{div} D\ \mathrm{grad} f + \iint dy\, dz \int_\pi^\pi d\omega \\ &\quad \big[K(y-z, \varphi + \tfrac{1}{2}\omega, \varphi - \tfrac{1}{2}\omega) f(y, \varphi + \tfrac{1}{2}\omega) f(z, \varphi - \tfrac{1}{2}\omega) \delta(\tfrac{1}{2}(y+z) - x) \\ &\quad - K(y-z, \varphi, \varphi - \omega) f(y, \varphi) f(z, \varphi - \omega) \delta(y - x)\big]\,. \end{aligned} \tag{11}$$

The second term on the right-hand side accounts for translational diffusion of the rods in the plane; D is the diffusion tensor, which is known from polymer physics. The integrals extend over all positions $y = (y_1, y_2)$ and $z = (z_1, z_2)$ in the plane and all orientation angles $\omega \in (-\pi, \pi)$. They represent the effect of molecular-mediated binary interactions (still assumed to be instantaneous) among the rods. Following an interaction, the two rods acquire the same orientation, as before, and their centers of mass occupy the same position midway between their positions prior to the interaction.

A reasonable first-order approximation of the kernel for a binary interaction of two rods whose centers of mass are located at the points y and z in the plane and whose orientation is given by

the angles φ and ψ, respectively, is

$$K(y-z,\varphi,\psi) = \frac{1}{\pi b^2}(1+\beta(y-z)\cdot(n_y-n_z))e^{-|y-z|^2/b^2}. \tag{12}$$

Here, b is a cutoff length (of the order of the length l of the rods), which limits the range of the interactions; n_y and n_z are the unit normal vectors along the rods; and β is a measure of the anisotropy of the interaction. The interaction of "diverging" rods is stronger than that of "converging" ones. The anisotropy, which is related to the fact that microtubules are polar filaments, varies considerably with the type and strength of the molecular motors; $\beta = 0$ if polarity is negligible.

The model (11) can be analyzed by the same techniques as the prototype model (1). The

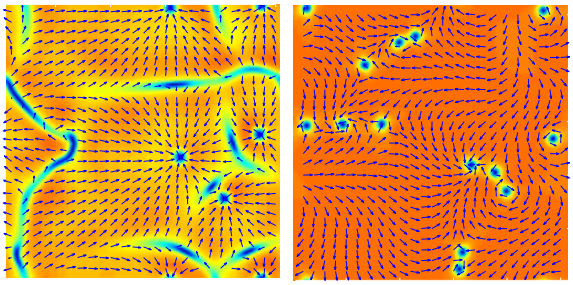

Figure 6: Orientation fields for asters (left) and vortices (right) near the threshold of instability [12].

analysis is more complicated, but a preliminary investigation has shown that the model exhibits an orientational instability as the density increases. Moreover, near the instability threshold, the system is well described by a reduced equation for the average orientation of the rods. Aster and vortex solutions, as well as transitions between these configurations, have been obtained for certain ranges of parameter values; see Fig. 6. Further investigations are under way.

Nonuniform Motor Densities The prototype model, as well as its localized version discussed in the previous section, assumed a spatially uniform distribution of the molecular motors. Clearly, if the microtubules organize themselves in patterns, the motor density will not be uniform; for example, one expects to find an increased density in the center of an aster, where more microtubules are concentrated. Experiments [5] have shown that, indeed, the motor density plays a critical role in morphogenetic processes.

Spatial variations of the motor density can be accounted for in the interaction kernel in the master equation. Instead of taking the kernel as in (12), one can take a kernel that depends not only explicitly on the difference $y-z$ but also implicitly on the coordinates y and z through the motor densities at these locations. The exact nature of this dependence can be determined independently by means of detailed molecular dynamics simulations, which can only be done computationally. One can then account for spatial variations in the motor density by coupling the master equation for the microtubules with a field equation for the motor density.

The model can be further generalized to account for the fact that molecular motors can have different "dwell times"—the time spent on a microtubule. For example, the molecular motors can be parameterized by their dwell times, and the kernel can be computed as a function of dwell time.

Microtubules as Filaments The prototype assumed that the microtubules could be modeled as stiff rods. In reality, microtubules are semiflexible filaments, which have a certain flexibility, and their stiffness can influence the potential for pattern formation on the macroscopic scale. The most direct way to account for this effect is to introduce the stiffness as another parameter characterizing the microtubules and compute the interaction kernel as a function of this parameter, again by means of detailed molecular dynamics simulations.

Other Effects Our models so far have been built on the assumption that we are dealing with an isolated mixture of microtubules and molecular motors. No external effects were included. Experiments [13] have shown that a molecular motor can attach to the surface of a container while its "free" end walks along a microtubule, resulting in "self-propelled" directed motion of the microtubule. Even a small fraction of absorbed motors can have a strong quantitative effect on self-assembly. The effect can be accounted for by adding an advective term to the master equation,

$$\partial_t f + \mathrm{div}(\alpha n f) = \mathrm{div}(D\mathrm{grad} f) + \partial_\varphi^2 f + Q(f; K). \tag{13}$$

Here, α is a coefficient proportional to the fraction of absorbed motors, n is the unit vector in the direction of the rod, and Q is the quadratic interaction term. The interaction kernel K incorporates the effects of the molecular motors.

In reality, cell structures are in constant motion, and it may be important to study the structural stability of any pattern, for example in an external flow. Such a generalization requires coupling the master equation with the equations of fluid flow (Navier–Stokes equations, or simplified versions thereof). Similar techniques have been applied to multiphase flows of mixtures of gases and granular materials [14].

Biological systems are by nature stochastic. Many of the variables and parameters that we have discussed so far are either not known or known only with a certain likelihood. Consequently, it is important to consider the structural stability of the models and, if possible, quantify the uncertainty of the predicted patterns of large-scale coherent organization.

1.1.3 The Ultimate Challenge

The ultimate goal of the proposed project is to shed light on the mechanism underlying pattern formation and self-organization at the cellular level. Clearly, cellular structures are three dimensional. Asters and vortices may be realistic in two dimensions, but they are only first approximations to reality, and our ultimate goal is to study ensembles of microtubules in three dimensions. Again assuming that microtubules can be modeled as stiff rods of fixed length and thickness, we need at least five variables to characterize a microtubule in three dimensions: the position of its center of mass, $x = (x_1, x_2, x_3)$, and the directional orientation of the rod, $\omega = (\varphi, \theta)$. Hence, the density

distribution of the microtubules is a function at least of x, ω, and t, and possibly other variables. A general master equation must account for changes caused by any of these variables. Hence, its simplest form is

$$\partial_t f = \mathrm{div}_x D_x \mathrm{grad}_x f + \mathrm{div}_\omega D_\omega \mathrm{grad}_\omega f + Q(f; K). \tag{14}$$

The first term in the right member refers to changes from diffusion in physical space, the second term to changes from orientational diffusion, and the last term to changes from binary interactions; as usual, the interaction kernel K incorporates the effects of the molecular motors. We recall that the latter appear only indirectly in the mesoscopic models, which are concerned solely with the microtubules.

Given the considerable complexity of fully three-dimensional problems, it is unlikely that we will be able to consider them in the scope of the proposed project. However, we expect to be able to investigate solutions with a special structure in three dimensions, such as the three-dimensional analog of the two-dimensional asters.

2 Research Program

The previous sections define the research program for the present proposal. The program focuses on the problem of pattern formation in mixtures of microtubules and molecular motors and takes a *multiscale approach*.

2.1 Multiscale Approach

The central concept in the proposed multiscale approach is that of a master equation on the mesoscale, which takes input from the microscale and, in turn, yields information on topological defects, such as asters and vortices, that may give rise to patterns on the macroscale.

Mesoscopic Scale The master equation describes the dynamics of an ensemble of interacting microtubules on the mesoscopic scale. The microtubules are characterized by their spatial position, orientation, and other parameters as appropriate. Information obtained on the microscopic scale is incorporated in the interaction kernel and accounts indirectly for the action of the molecular motors.

The purpose of a description at the mesoscopic level is to determine regimes where instabilities may arise, identify the nature of these instabilities, and compare the results with the solution of the coarse-grained equations on the macroscopic scale.

The code developed for simulations on the basis of the prototype model (1) and its generalization (11) will be hardened and extended in the directions outlined in Section 1.1.2. Extensions under consideration will address the fact that the outcome of a motor-induced interaction among two microtubules may depend on their mutual distance and orientation prior to the interaction.

Further extensions will address nonuniform motor densities, the modeling of microtubules as flexible elastic filaments, and advection effects from absorption of molecular motors. We will determine the proper formulation of stochastic effects by lifting the latter from the microscopic to the mesoscopic scale and will include them in the models, for example, directly through a Langevin formulation or indirectly by introducing random parameters in the various coefficients.

The computational studies will be complemented with analysis where appropriate. The purpose here is to analyze the various approximations and determine their domain of validity. For example, to arrive at the prototype model (1), we assumed without justification that higher harmonics of the density function could be ignored and that its first and second harmonic evolved on different time scales. Such assumptions need to be verified. As part of the proposed project, we will develop a mathematical framework for the analysis of general master equations like Eq. (14). This part of the analysis will build on recent work in the kinetic theory of gases [15].

Once a mathematical framework has been developed, one can analyze the approximations inherent in the models, determine their domain of validity, and suggest alternatives where appropriate. The same framework can be used to analyze the numerical approximations underlying the computational algorithms.

Bifurcation analysis at the level of the master equation will enable us to identify parameter regimes where instabilities may arise and provide insight into the nature of these singularities. For example, by considering two-dimensional solutions of the model (11) with particular symmetries, we were able to explore parameter space and identify regions where asters and vortex solutions could be anticipated. Information of this type is essential for the derivation of the reduced models that will be studied at the macroscopic level.

Microscopic Scale On the microscopic scale, molecular dynamics simulations will be used to characterize the elementary interactions of microtubules and molecular motors. The simulations suggest and verify functional forms for the interaction kernels for the microtubules adopted at the level of the master equation. The simulations also quantify the parameters and the influence of stochastic effects on these interaction kernels.

The code used for the molecular dynamics simulations will be based on publicly available software developed by researchers at the University of Heidelberg (CYTOSIM [16]). In CYTOSIM, microtubules are modeled as semiflexible rods interacting with motors. Motors are characterized by their velocity, strength, detachment/attachment probability, and diffusion coefficient.

The project will require an extension of the code to enable fully three-dimensional simulations, parameter variations, and stochastic effects. Additional modifications under consideration will address the attachment of molecular motors to the substrate and the effects of external forces in fluid flow. The last case is especially challenging because it involves the computation of a drag force from simulations of the coupled equations for microtubular motion and hydrodynamic flows.

Macroscopic Scale On the macroscopic scale, the focus is on coarse-grained quantities. In general, we are dealing with "amplitude equations," systems of a few nonlinear differential equations

for the first few orientational moments of the density distribution function. Amplitude equations can be derived systematically from the master equation and provide a reduced description of the system near critical points (for example, where orientational phase transitions occur). The main thrust of the research at this level is the identification of the critical points and the derivation and analysis of the amplitude equations. Critical points are generically associated with bifurcation phenomena and pattern formation, which are the essence of the process of self-organization. The investigations at the macroscopic scale involve both analysis and computations.

2.2 Computational Challenges

The proposed project has the hallmark features of a state-of-the-art computational science project. It addresses a multiscale problem requiring three levels of description, and the major challenge is to couple the computations at the three levels in an efficient manner. Multiscale computations will constitute a major component of the project.

The description of the biological system is anchored at the middle (mesoscopic) level, where one needs to integrate a master equation that involves at least three independent variables (two space variables and one orientational variable) besides time. The master equation itself requires the specification of an interaction kernel obtained from simulations at the microscopic level. The integration of the master equation must cover a sufficiently long time interval so that possible instabilities and phase transitions can be identified with some degree of confidence. Once these instabilities have been identified, details are found from simulations at the macroscopic level.

We propose an equation-free approach [17] to validate the approximation of binary interactions at the mesoscopic level and the use of coarse-grained equations at the macroscopic level.

The computational requirements necessarily impose a severe constraint on the size of the spatial domain that can be accommodated. The challenge here is to design a discretization method that balances the need for spatial resolution with the need to see long-term trends in the temporal evolution of the system. We intend to apply domain decomposition techniques and develop higher-order approximations (such as spectral elements) to reduce the number of degrees of freedom. Domain decomposition techniques apply to the equations at both the mesoscopic and the macroscopic level.

The implementation will be based upon PETSc [18], a scalable software package for the solution of partial differential equations on parallel architectures. Developed at Argonne, PETSc has a proven record of enabling computational science on massively parallel computers.

The recent acquisition of a 2,048-processor Blue Gene/L supercomputer by Argonne National Laboratory provides an ideal implementation platform to meet the challenges outlined above. Blue Gene, whose architecture was motivated by the protein-folding problem, emphasizes the efficient computation of long-range interactions, as encountered in molecular dynamics, and the ability to integrate over increasingly long times. Thus it is well tuned to the computational needs of the proposed project. Its low-latency three-dimensional torus network supports the efficient solution of the master equation in two spatial dimensions (which involves three independent variables), as well as the coarse-grained equations derived from the master equation in three spatial dimensions.

3 Impact of the Project

The ultimate goal of the project is to shed light on the formation of large-scale coherent structures in biological systems. For example, in eukaryotic cells, the intracellular architecture is determined to a large extent by the collective behavior of the ensemble of proteins that constitute the cytoskeleton. Motor proteins and filaments are known to play an important role in determining the final structure, but how their concentrations and the combination of plus- and minus-end motors contribute to the morphogenetic process is not understood. Experiments in highly simplified biological systems [1, 2] have revealed a rich variety of self-assembled static and dynamic configurations. The current project will advance our understanding of the results of these experiments and will stimulate further research in meaningful and interesting directions.

We also expect that the proposed project will benefit the new discipline of computational science. The problem under consideration is a fascinating multiscale problem, with significant computational complexity at all three levels. The integration of numerical simulations at different levels of detail will be a major challenge, and lessons learned here will be applicable to other problems of computational science.

The investigators expect to interact closely with the authors of PETSc (who are at the same institution as three of the PIs on the proposed project) and thus provide feedback that might benefit future developments of this major computer science project.

Impact on physics can be expected because molecular dynamics simulations are an integral part of the project. Lessons learned in the project will advance the case for integration of molecular dynamics simulation codes in future multiscale environments.

The project will have educational benefits as well because it involves graduate students and a junior researcher.

Outreach will consist of the usual means of dissemination through publications in the professional literature and presentations at technical meetings.

4 Program Personnel

Principal Investigator:

- Hans G. Kaper, Senior Scientist, Mathematics and Computer Science Division, ANL

  Areas of expertise: Applied mathematics, differential equations, asymptotic analysis, scientific computing

Consultants:

- Igor Aronson, Scientist, Materials Science Division, ANL

Areas of expertise: Condensed matter physics, granular media, biodynamics, scientific computing

- Lev S. Tsimring, Research Scientist, Institute for Nonlinear Science, UCSD

  Areas of expertise: Condensed matter physics, granular materials, pattern formation, biodynamics

Postdoctoral Scholar: Dmitry Karpeev, Ph.D., computer science, Old Dominion University (2002); Mathematics and Computer Science Division, ANL

Research Associates: A proposal similar to the present one has been submitted to the National Science Foundation, CISE Directorate, Division of Computing and Communication Foundations in response to Program Solicitation NSF05-501. This proposal includes a request for graduate student support at UCSD.

5 Computing Resources

The proposed project will rely heavily on the computing facilities available at ANL, which include a recently acquired 1,024-node (2,048-processor) single-rack Blue Gene/L supercomputer [19] and a 350-node Linux cluster. We intend to join the Argonne-based Blue Gene Consortium [20], a user group dedicated to the development of Blue Gene/L applications and systems software.

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2. T. Surrey, M. B. Elowitz, P.-E. Wolf, F. Yang, F. J. Nédélec, K. Shokat, and S. Leibler, *Science* **292**, 1167 (2001)
3. H. Y. Lee and M. Kardar, *Phys. Rev. E* **64**, 056113 (2001)
4. J. Kim, Y. Park, B. Kahng, and H. Y. Lee, *J. Korean Phys. Soc.* **42**, 162 (2003)
5. F. Nedelec, T. Surrey, and A. C. Maggs, *Phys. Rev. Lett.* **86**, 3192 (2001)
6. S. Sankararaman, G. I. Menon, and P. B. Sunil Kumar, *Phys. Rev. E* **70**, 031905 (2004)
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10. S. Chapman and T. G. Cowling, *The mathematical theory of non-uniform gases*, Cambridge University Press (1952)

11. J. H. Ferziger and H. G. Kaper, *Mathematical theory of transport processes in gases*, North-Holland Publ. Comp., Amsterdam (1972)

12. I. S. Aronson and L. S. Tsimring, Pattern formation of microtubules and motors: interaction of polar rods, manuscript in preparation

13. R. D. Vale and R. A. Milligan, *Science* **288**, 88 (2000)

14. D. Gidaspow, *Multiphase Flow and Fluidization: Continuum and Kinetic Theory Descriptions* Academic Press, Boston (1994)

15. B. Perthame, *Bull. Am. Math. Soc.*, **41**,205–244 (2004)

16. F. J. Nédélec et al., Cell Biology and Biophysics Program, University of Heidelberg, Germany (www.embl-heidelberg.de/ExternalInfo/nedelec/cytosim/index.html)

17. C. W. Gear and I. G. Kevrekidis, *J. Sci. Comp.* (in press, 2004); also physics/0312094 at arXiv.org

18. S. Balay, et al., *PETSc Users Manual*, *ANL-95/11 - Revision 2.1.5* Argonne National Laboratory (2004) (http://www.mcs.anl.gov/petsc)

19. http://www.research.ibm.com/bluegene

20. http://www.mcs.anl.gov/bgconsortium

Igor S. Aronson

Professional Preparation

1987	Academy of Science, Institute of Applied Physics, Gorky, Russia, Ph.D. Physics
1982	Gorky State University, Russia, M.Sc. Physics (Summa Cum Laude)
1981	Gorky State University, Russia, B.Sc. Physics

Appointments

1999–present	Staff Physicist, Argonne National Laboratory
1996–99	Visiting Scientist, Argonne National Laboratory
1993–96	Senior Lecturer, Bar Ilan University, Israel
1991–93	Research Associate, The Hebrew University of Jerusalem
1987–91	Research Associate, Institute of Applied Physics, Gorky, Russia
1982–86	Junior Research Associate, Research Institute of Microelectronics, Gorky, Russia

Relevant Publications

1. I. S. Aranson and L. S. Tsimring, "Model of Coarsening and Vortex Formation in Vibrated Granular Rods," *Phys. Rev. E*, **67**, 021305 (2003)

2. M. V. Sapozhnikov, Y. V. Tolmachev, I. S. Aranson, and W.-K. Kwok, "Dynamic Self-Assembly and Patterns in Electrostatically Driven Granular Media," *Phys. Rev. Lett.*, **90**, 114301 (2003)

3. I. S. Aranson and M. V. Sapozhnikov, "Theory of Pattern Formation of Metallic Microparticles in Poorly Conducting Liquid," *Phys. Rev. Lett.*, *90*, 114301 (2004)

4. M. V. Sapozhnikov, I. S. Aranson, W.-K. Kwok, and Y. V. Tolmachev "Self-Assembly and Vortices Formed by Microparticles in Weak Electrolytes," *Phys. Rev. Lett.*, *93*, 084502 (2004)

5. I. S. Aranson and L. S. Tsimring, "Pattern Formation of Microtubules and Motors: Inelastic Interaction of Polar Rods," *Phys. Rev. Lett.*, submitted (2004)

Other Publications

1. I. S. Aranson and L. S. Tsimring, "Continuum Description of Avalanches in Granular Media," *Phys. Rev. E*, *64*, 020301 (2001)

2. J. Li, I. S. Aranson, W.-K. Kwok, and L. S. Tsimring, "Periodic and Disordered Structures in a Modulated Gas-Driven Granular Layer," *Phys. Rev. Lett.*, *90*, 134301 (2003)

3. D. Volfson, L. S. Tsimring, and I. S. Aranson, "Order Parameter Description of Stationary Partially Fluidized Shear Granular Flows," *Phys. Rev. Lett.*, *90*, 254301 (2003)

4. D. Volfson, L. S. Tsimring, and I. S. Aranson, "Stick-Slip Dynamics of a Granular Layer Under Shear," *Phys. Rev. E*, *69*, 031302 (2004)

5. I. S. Aranson and L. Kramer, "The World of Complex Ginzburg-Landau Equation," *Rev. Mod. Phys.*, *74*, 99-143 (2002)

Synergistic Activities

1. Organizer and Scientific Director, EuroSummer School and NATO Advanced Studies Institute on "Pattern Formation, Granular Physics and Soft Condensed Matter," Benasque, Spain, Sept. 4–Oct. 8, 2003

2. Co-Organizer, NATO Advanced Studies Institute on "Self-Assembly, Pattern Formation and Growth Phenomena in Nano-Systems," St. Etienne de Tinee, France, Aug. 28–Sep. 12, 2004

Collaborators in past 48 months

E. Ben-Naim (LANL), H. Chate (CEA, France), E. Clement (ESPCI, France), G. W. Crabtree (Argonne), A. Golovin (Northwestern), A. Gurevich (U Wisconsin), H. Kaper (Argonne), A. Koshelev (Argonne), Wai Kwok (Argonne), B. Meerson (Jerusalem, Israel), J. Olafsen (U Kansas), A. Peleg (LANL), Y. Tolmachev (Kent University), L. Tsimring (UCSD), V. Vinokur (Argonne), V. Vlasko-Vlasov (Argonne), D. Volfson (UCSD), U. Welp (Argonne)

Advisors

Graduate: Prof. Mikhail Rabinovich (now at UCSD)
Postdoctoral: Prof. Lorenz Kramer (University of Bayreuth, Germany)

Graduate Students Supervised (total of 2)

Gogi Singh (Northwestern University)
Kevin Kohlstedt (University of Kansas)

Postdoctoral Associates Supervised (total of 6)

Maksim Sapozhnikov, Institute of Physics for Microstructures, Russia (2004);
Jie Li, Argonne (2004);
Alexei Snezhko, Argonne (2004);
Valerii Kalatski, University of San-Francisco (2001);
Daniel Howell, now at Naval Analysis Inc. (2001);
Daniel Blair, Harvard University (2000)

Honors and Awards

Gold Medal, All-Union (USSR) competition of M.Sc. theses (1982)
Alexander-von-Humboldt Fellowship, Germany (1991)
Wolfson Research Fellowship, Israel (1991)
Guastello Research Fellowship, Israel (1993)
Fellow, American Physical Society, Division of Condensed Matter Physics (2002)

Hans G. Kaper

Professional Preparation

1965	Rijksuniversiteit Groningen, Netherlands, Ph.D. Mathematics and Physical Sciences (cum laude)
1960	Rijksuniversiteit Groningen, Netherlands, M.Sc. Mathematics and Physical Sciences
1957	Rijksuniversiteit Groningen, Netherlands, B.Sc. Mathematics and Physical Sciences

Appointments

2000–present	Sr. Fellow, Computation Institute, The University of Chicago
1982–present	Sr. Mathematician, Argonne National Laboratory
2001–04	Program Director, National Science Foundation
1987–91	Director, Mathematics and Computer Science Division, Argonne National Laboratory
1969–92	Mathematician, Argonne National Laboratory
1967–69	Associate Professor, University of Groningen, Netherlands
1965–67	Assistant Professor, University of Groningen, Netherlands

Visiting and Temporary Positions

Adjunct Professor	University of Illinois at Urbana-Champaign (School of Music), 2004–present
Visiting Professor	Université Bordeaux 1, Bordeaux, France, 2000
Visiting Professor	Université Toulouse I, Toulouse, France, 1995
Visiting Professor	Université Claude Bernard, Lyon, France, 1993
Adjunct Professor	Northern Illinois University, 1982–92
Visiting Professor	Northwestern University, 1978–80, 1984–85
Visiting Professor	Universität Wien, Vienna, Austria, 1976–77
Visiting Professor	Universiteit van Amsterdam, 1976–77
Sr. Scientific Officer	Mathematisch Centrum, Amsterdam, 1976–77
Research Associate	Stanford University, 1966–67

Relevant Publications

1. A. Zagaris, H. G. Kaper, and T. J. Kaper, "Fast and Slow Dynamics for the Computational Singular Perturbation Method," *Multiscale Modeling and Simulation* **2** (2004) 613–638

2. H. G. Kaper, C. G. Lekkerkerker and J. Hejtmanek, *Spectral Methods in Linear Transport Theory*, Birkhäuser Verlag, Basel, 1982

3. J. H. Ferziger and H. G. Kaper, *Mathematical Theory of Transport Processes in Gases*, North-Holland Publ. Company, Amsterdam, 1972

Other Publications

1. A. Zagaris, H. G. Kaper, and T. J. Kaper, "Two Perspectives on Reduction of Ordinary Differential Equations," *Math. Nachrichten* (to appear)

2. A. Zagaris, H. G. Kaper, and T. J. Kaper, "Analysis of the Computational Singular Perturbation Reduction Method for Chemical Kinetics," *J. Nonlinear Science* **14** (2004) 59–91

3. H. G. Kaper and T. J. Kaper, "Asymptotic Analysis of Two Reduction Mechanisms for Systems of Chemical Reactions," *Physica D* **165** (2002) 66–93

4. T. Colin, C. Galusinski, and H. G. Kaper, "Waves in Ferromagnetic Media," *Communications in PDEs* **27** (2002) 1625–1658

5. J. S. Jiang, H. G. Kaper, and G. K. Leaf, "Hysteresis in Layered Spring Magnets," *Discrete and Continuous Dynamical Systems – Series B* **1** (2001) 219–232

Synergistic Activities

1. Program Director, Applied and Computational Mathematics, Division of Mathematical Sciences, National Science Foundation (2001–04)

2. Chairman, QANU/Research Assessment of Mathematics, under the auspices of the Royal Netherlands Academy of Arts and Sciences (2003; report published August 2004)

3. Member, Committee of Visitors, Division of Mathematical Sciences, NSF (2001)

4. Co-Chairman, Theory Institute *Dimension Reduction for Chemical Kinetics* Argonne (2000)

5. Associate Editor: Integral Equations and Operator Theory, Transport Theory and Statistical Physics, J. of Engineering Mathematics; Editor-at-Large: Applied Mathematics, Marcel Dekker, Inc.

Collaborators in past 48 months

I. S. Aronson (Argonne), T. Colin (University of Bordeaux I), M. J. Davis (Argonne), C. Galusinski (University of Bordeaux I), M. Garbey (University of Houston), M. Grimsditch (Argonne), J. Guessford (UIUC), T. J. Kaper (Boston University), D. A. Karpeev (Argonne), G. K. Leaf (Argonne), S. Tipei (UIUC), S. Wang (Indiana University), A. Zagaris (Boston University)

Advisors

Graduate: Prof. A. I. van de Vooren (University of Groningen)
Postdoctoral: Prof. J. H. Ferziger (Stanford University, deceased)

Students and Postdocs Supervised

None officially, but I regularly supervise participants in Argonne's Research Participation Programs for undergraduate and graduate students and work on a daily basis with the postdocs in Argonne's MCS Division.

Honors and Awards

Corresponding member, Royal Netherlands Academy of Arts and Sciences
NATO Science Fellowship, 1966–67
EURATOM Research Fellowship, 1961

Dmitry A. Karpeev

Professional Preparation

2002 Old Dominion University, Ph.D. Computer Science
1996 Old Dominion University, B.Sc. Applied Mathematics (Summa Cum Laude)

Appointments

2002–present Postdoctoral Researcher, Argonne National Laboratory
2000-2002 Givens Fellow, Argonne National Laboratory

Publications

1. M. Grimsditch, G. K. Leaf, H. G. Kaper, D. A. Karpeev, R. E. Camley, "Normal Modes of Spin Excitations in Nanoparticles," *Phys. Rev. B* (to appear)
2. D. A. Karpeev and C. M. Schober, "Local Lagrangian Formalism and Discretization of the Heisenberg Magnet Model," *Mathematics and Computers in Simulation* (to appear)
3. A. L. Islas, D. A. Karpeev, and C. M. Schober, "Geometric Integrators for the Nonlinear Schrödinger Equation," *J. Comp. Phys.* **173** (2001) 116–148
4. D. A. Karpeev and C. M. Schober, "Symplectic Integrators for Discrete Nonlinear Schrödinger Systems," *Mathematics and Computers in Simulation*, **56(2)** (2001) 145–156

Collaborators in past 48 months

R. E. Camley (U Colorado at Colorado Springs), M. Grimsditch (Argonne), A. Islas (U Central Florida), H. G. Kaper (Argonne), D. E. Keyes (Columbia U), M. G. Knepley (Argonne), G. K. Leaf (Argonne), C. M. Schober (U Central Florida), E. E. Selkov (Argonne)

Advisors

Graduate: Prof. D. E. Keyes (now Columbia), Prof. C. M. Schober (now U Central Florida)
Postdoctoral: Dr. E. E. Selkov (Argonne)

Honors and Awards

Outstanding Graduating Senior, Mathematics Department, Old Dominion University (1996)
GAANN Fellowship, USA, Germany (1996–2002)
Givens Fellowship, Argonne, USA (2000)

Lev S. Tsimring

Professional Preparation

1985 Institute of Applied Physics, Gorky, Russia, Ph.D. Physics
1980 Gorky State University, Russia, M.Sc. Physics

Appointments

1992–present Research Scientist, University of California, San Diego
1980–91 Research Scientist, Institute of Applied Physics, Gorky, Russia

Relevant Publications

1. D. Volfson, L. S. Tsimring, and A. Kudrolli, "Anisotropy driven dynamics in vibrated granular rods," *Phys. Rev. E*, **70**, 051312 (2004)

2. D. Volfson, L. S. Tsimring and I .S. Aranson, "Order parameter description of stationary partially fluidized shear granular flows," *Phys. Rev. Lett.*, **90**, 254301 (2003)

3. I. S. Aranson and L. S. Tsimring, "Dynamics of the constrained polymer collapse, *Europhysics Letters*, **62(6)**, 848-854 (2003) A

4. I. S. Aranson and L. S. Tsimring, "Model of coarsening and vortex formation in vibrated granular rods, cond-mat/0203237, *Phys. Rev. E*, **67**, 021305 (2003)

5. A. M. Delprato, A. Samadani, A. Kudrolli, and L. S. Tsimring, "Swarming ring patterns in bacterial colonies exposed to ultraviolet radiation, *Phys. Rev. Lett.*, **87**, 158102 (2001)

Other Publications

1. H. D. I. Abarbanel, R. Brown, J .J. Sidorowich, and L. S. Tsimring, "The analysis of observed chaotic data in physical systems," *Rev. Mod. Phys.*, **64(5)**, 1331-1393 (1993)

2. N. F. Rulkov, M. M. Sushchik, L. S. Tsimring, H. D. I. Abarbanel, "Generalized synchronization of chaos in directionally coupled chaotic systems," *Phys. Rev. E*, **51(2)**, 980-994 (1995)

3. E. Ben-Jacob, I. Cohen, O. Shochet, I. S. Aranson, H. Levine, L. S. Tsimring, "Complex bacterial patterns," *Nature*, **373** (6515), 566 (16 February 1995)

4. H. Levine, I. Aranson, L. Tsimring and T. Truong, "Positive genetic feedback governs cAMP spiral wave formation in Dictyostelium," *Proc. Natl. Acad. Sci. USA*, **93**, 6382-6386 (1996)

5. L. S. Tsimring and A. S. Pikovsky, "Noise-induced dynamics in bistable systems with delay," *Phys. Rev. Lett.*, **87**, 250602 (2001)

Synergistic Activities

1. Associate Director, Institute for Nonlinear Science, UCSD, 2000-present
2. Organizer, Annual Winter Schools in Communications With Chaos, 1999-2003
3. Co-chair, Gordon Research Conference on Granular and Granular–Fluid Flow, 2002

Collaborators in past 48 months

H. D. I. Abarbanel (UCSD), I. S. Aranson (Argonne), J. Hasty (UCSD), L. Larson (UCSD), D. Huber (UCSD), R. Huerta (UCSD), A. Kudrolli (Clark), A. Pikovsky (Potsdam), M. Rabinovich (UCSD), N. F. Rulkov (UCSD), R. Tenny (UCSD), V. M. Vinokur (Argonne), D. Volfson (UCSD), A. Volkovskii (UCSD)

Advisors

Graduate: L. A. Ostrovsky (Gorky State University, Institute of Applied Physics), B M. I. Rabinovich (Institute of Applied Physics, currently at UCSD)

Graduate Students Supervised (total of 1)

Y. Nikolaeva (Institute of Applied Physcs, Gorky)

Postdoctoral Associates Supervised (total of 7)

M. Sushchik (Thermowave),
L. Korzinov (UCSD),
G.-M. Maggio (UCSD),
D. Volfson (UCSD),
A. Volkovskii (UCSD),
R. Tenny (UCSD),
Z. Tazev (UCSD)

Undergraduate Research Students

D. K. Clark, S. C. Young, P. Seliger (UCSD)

Budget

The duration of the proposed project is 36 months, with a requested starting date of July 1, 2005.

The annual budget covers the following personnel:

Researcher	**Effort**
Hans Kaper	0.5 FTE
Dmitry Karpeev	0.5 FTE
Graduate Student	1.0 FTE

The project receives additional funding from DOE for Igor Aronson (Materials Science program, 1.0 FTE).

A similar proposal for the same project has been submitted through the University of Chicago to NSF (CISE/CCF) in response to solicitation 05-501 (Emerging Models and Technologies for Comnputation), requesting support for Igor Aronson (0.5 month), Hans Kaper (0.5 month), Dmitry Karpeev (6 months), and one graduate student.